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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,025	04/27/2001	Jennifer Ott Reilly	CIBT-P01-098	1533

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/845,025	REILLY, JENNIFER OTT	
	Examiner	**Art Unit**	
	Michael Brannock	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 08 November 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *01 November 0804*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): See Attachment to Advisory Action.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see Attachment*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1-4*.

Claim(s) withdrawn from consideration: *5, 10, 13-28*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Attachment to Advisory Action

Applicant is notified that the amendments put forth on 11/08/04 have been entered in full.

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments.

Claim 1 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

As set forth previously, the recitation of the term " hedgehog polypeptide" without reference to a particular amino acid or nucleic acid sequence renders the claims indefinite because the specification has not put forth that material or functional element that is indicative of a "hedgehog polypeptide" and nor is such a definition known in the prior art which clearly sets forth which polypeptides are hedgehog polypeptides and which are not. Therefore the metes and bounds of the claims cannot be determined.

The examiner agrees that one skilled in the art would understand the metes and bounds of what would be called a naturally occurring sonic hedgehog polypeptide, yet the claims are not so limited, i.e. the claim merely requires that the hedgehog polypeptide comprise a naturally occurring sequence. Thus this sequence could be only two amino acids in length and would say nothing about what else might comprise the hedgehog polypeptide.

Claim 1 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of promoting the survival of cholinergic neurons, comprising the administration of a naturally occurring mammalian sonic hedgehog polypeptide (e.g. SEQ ID NO: 15) or the N-terminal autoproteolytic fragment thereof, does not reasonably provide enablement for such methods comprising the administration of polypeptides other than a naturally occurring mammalian sonic hedgehog polypeptides. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims, as set forth previously.

As set forth above, the claim is not limited to naturally occurring mammalian sonic hedgehog polypeptides as alleged by Applicant.

Claims 1-4 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No: 5884079 to Ingham et al., in view of Molses et al., Journal of Neuroscience 15(12)8131-8142)1995, as set forth previously and reiterated below.

The specification discloses that administration of hedgehog proteins along with certain neurotrophic factors can promote the survival of a variety of neuron cell types, each of which are known in the art to be lost in particular neurodegenerative diseases, e.g. Parkinson, Huntington, and Alzheimer's diseases. A specific embodiment of the instant claims is a method of promoting the survival of cholinergic neurons of the basal forebrain, either *in vivo* or *in vitro*, comprising the co administration of the N-terminal autoproteolytic fragment of sonic hedgehog (e.g. residues 24-197 of SEQ ID NO: 15) and nerve growth factor (NGF) e.g. pages71-75. The specification indicates that such neurons are known to degenerate in Alzheimer's disease, e.g. pages 62-63,

and that these neurons are also useful for *in vitro* studies regarding the effects of neurotrophic factors on them (particularly the effect of sonic hedgehog), as is well established in the art. e.g. see page 71.

U.S. Patent No: 5884079 also discloses that the above disorders and associated neurons can be treated with the N-terminal autoproteolytic fragment of sonic hedgehog (e.g. col 46) and that such treatment can be in combination with the administration of an appropriate neurotrophic factor, e.g. CNTF, BDNF or NGF, see col 47, Lines 27- 38. More particularly U.S. Patent No: 5884079 discloses that cholinergic neurons of the basal forebrain (those of the nucleous basalis), that degenerate in Alzheimer's disease, can be treated with sonic hedgehog proteins (col 46, L38-47). U.S. Patent No: 5884079 does not, however, specifically state which additional neurotrophic factors would be appropriate to use in the context of Alzheimer's disease. Specifically, U.S. Patent No: 5884079 does not disclose that NGF is trophic for the cholinergic neurons of the basal forebrain as is required by the embodiment of the instant claims referred to above. However, an artisan of ordinary skill appreciates that the survival-promoting effects of NGF on cholinergic neurons of the basal forebrain is well established and old in the art, see Molses et al. who teach that treatment of rats *in vivo* with NGF promotes the survival of basal forebrain cholinergic neurons (see the Abstract).

Therefore, it would be obvious to one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, to promote the survival of cholinergic neurons of the basal forebrain (nucleous basalis) by administering a trophic amount of the autoproteolytic fragment of sonic hedgehog and another appropriate neurotrophic factor including CNTF, BDNF and NGF, as taught and suggested by Patent No: 5884079 (cols 46-47)

and to use NGF as the particular neurotrophic factor as taught by Molses et al. The motivation to do so is provided by Patent No: 5884079 wherein it is taught that neuronal degenerative disorders such as Alzheimer's disease can be treated with sonic hedgehog in combination with appropriate neurotrophic factors (cols 46-47) and Molses et al. who teach that NGF is an appropriate factor to use on the particular neurons involved in Alzheimer's disease, e.g. the cholinergic neurons of the basal forebrain, see the Abstract.

Applicant argues that the instant claims are unobvious species of the genus taught by Patent No: 5884079 and that neither reference provides the motivation to provide the particular elements recited in the claims. This argument has been fully considered but not deemed persuasive. As set forth above, Patent No: 5884079 specifically teaches the use of sonic hedgehog with NGF for promoting the survival of neurons, including cholinergic neurons. Molses teach that treatment of rats *in vivo* with NGF promotes the survival of basal forebrain cholinergic neurons. Therefore it would be obvious to treat cholinergic neurons with sonic hedgehog and NGF. That these two factors would act synergistically would not need to be anticipated by one skilled in the art to be motivated to use them together, because their use together is taught and suggested by the combination of Patent No: 5884079 and Molses.

As stated previously, this application contains claims 5, 10, 13-28 drawn to an invention nonelected with traverse in Paper No 17. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Conclusion

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D., can be reached at (571) 272-0829. Official papers filed by fax should be directed to 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH M[illegible]
PRIMARY EXAMINER

MB

January 24, 2005